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SPECIAL ELECTROPHYSIOLOGICAL TESTS:

Brain Spiking, EEG Spectral Coherence

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INTRODUCTION

Largely as a consequence of advances in computer technology the use of time series analysis methodology to investigate correlations of brain electrical activity with clinical disorders has become an area of intense effort in many EEG research laboratories. The primary objective of many of these investigations is the detection of EEG time series properties which offer a quantitative basis for aiding diagnosis of mental illness or brain injury. This chapter describes the special electrophysiological tests which we have been developing at TRIMS* for application to research projects concerned with the detection of EEG properties which correlate with particular abnormalities such as uncontrolled violent behavior, learning disabilities and epilepsy.

BRAIN SPIKING

Intermittent deep brain electrical spiking as well as scalp EEG spiking has been implicated in certain brain and behavioral disorders such as epilepsy[1] and uncontrolled violent behavior. The correlation of abnormal deep brain electrical spiking activity with violent behavior has been demonstrated in nonhuman primate studies[2] by employing invasive methods which involve the surgical implantation of electrodes and subsequent analysis of the electrical activity recorded from the implanted deep brain structures. In light of these results, a significant advancement in the

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diagnosis of abnormal brain activity, especially that deep brain activity associated with persons exhibiting uncontrolled violent behavior, would be achieved by the development of detection methods that are noninvasive and therefore applicable in ordinary clinical EEG settings.

Our EEG research on noninvasive detection was stimulated primarily by the initial finding of complex patterns of consistent waveshape in scalp EEG which were time-locked to spikes recorded from electrodes implanted in deep brain structures of rhesus monkeys. These studies[2] have also shown that such scalp correlates of deep spiking can be detected even in severe EEG noise backgrounds by the application of digital filters appropriately designed to minimize the effects of unwanted EEG background activity, or by special application of cepstral methods in cases where digital filters for pattern recognition are not suitable because the pattern to be detected is not known a'priori. The analytical methods and their potential applications are described in references[3][4][5][6].

DETECTION METHODS

The digital filtering procedures developed for detecting scalp correlates of deep spiking were based on an analysis of monkey and human scalp EEG data obtained from research projects where simultaneous recordings from deep brain structures were available. Using the deep spike as the trigger for averaging

scalp EEG activity, it was observed that transient slow wave activity frequently appeared in scalp activity at the same time that a spike occurred at depth. The waveshape of this transient activity was usually distorted by the presence of noise; therefore averaging procedures were used to achieve a better estimate of the transient waveshape. The power spectral density of the scalp EEG background activity was also estimated in order to appropriately weight the spectral components in the transient waveshape obtained by averaging. The digital filter derived from the spectral estimates of both the transient waveshape and the noise was employed as a detector which looks at scalp activity and reports on the presence or nonpresence of transient patterns which match the characteristics of the digital filter. It is interesting to note that this coincidence of deep spiking and transient EEG slowing implies that pathological sharp spiking activity at depth produces slow wave activity at the surface. This is consistent with clinical EEG criteria which consider focal slow activity to be an abnormal indication.

The procedure for evaluating candidate digital filters was based on the number of spikes detected in normal subjects as compared to the number of spikes detected in the recording of mentally ill subjects. In the initial evaluation a comparison was made of the incidence of spikes in normals and in violent subjects, based on a Poisson model for random spiking. In this

model the number of spikes detected over a given length of recording is compared with the expected number derived from data on normals. The normal control is used to test the hypothesis that a given record represents the EEG of a normal subject under the assumption that spikes in normal subjects are uniformly randomly distributed. The methods of analysis underlying these evaluation procedures depend on the performance characteristics of the digital filter as a detector, as well as on the statistical model for evaluating the significance of the number of spikes detected. These methods are described in the next section.

COMPUTER IMPLEMENTATION

By virtue of our computer configuration, Fourier series methods (rather than matrix inversion methods) were used to design as well as evaluate the digital filter. The Fourier methods for the design of the optimum filter proceed as follows:

1. Obtain (a) the complex Fourier series of the candidate transient patterns and, (b) the power spectral density of the signal plus noise; that is, the background EEG signal.
2. Divide the conjugate complex Fourier series of the transient pattern by the power spectral density of the signal plus noise.
3. Take the inverse transform of the Fourier series obtained in Step 2 which gives a discretely sampled time function that is the desired template or matched filter.

In addition to performing the above operations, the computer in our laboratory is also capable of performing running convolution. This allows continuous digital filtering of the scalp EEG to rapidly evaluate the performance characteristics of a candidate digital filter as a detector of abnormal transient activity.

The above analytical procedures refer to the detection of spike induced events, but it is necessary to assign some significance to the number of events detected in terms of background activity and artifacts that produce false spike indications. The major difficulty which presents itself in physiological signal studies of this type arises from the fact that any given signal characteristic such as a spike can and usually does appear due to random background effects. The problem then becomes one of determining whether the appearance of this signal characteristic is due to background effects or to some inherent neurophysiological abnormality in the EEG being analyzed. The analysis and evaluation rationale are straightforward if it is assumed that the time interval between spike indications is random and uniformly distributed due to background activity in the normal EEG. With the foregoing assumptions, the analysis proceeds as follows:

let $p_n(t)$ = probability of exactly n spikes occurring in time t due to EEG background activity in normal subjects and,

$p_n(t+\Delta t)$ = probability of exactly n spikes occurring in time $t+\Delta t$ due to EEG background activity in normal subjects and,

λ = average rate at which spikes occur in the EEGs of normal control subjects;

then $p_n(t+\Delta t) = p_n(t)(1-\lambda\Delta t) + p_{n-1}(t)\lambda\Delta t.$ (1)

Equation (1) states (a) that the probability of exactly n spikes occurring over $t+\Delta t$ is equal to the probability that n spikes occur over time t and none in Δt, plus the probability that exactly $(n-1)$ spikes occur over time t and exactly one in Δt and that the time increment Δt is so small that (b) the probability of two or more spikes occurring during Δt is zero, and (c) that the probability of one spike occurring at Δt is $\lambda\Delta t$. Rearranging terms in Equation (1), and passing to the limit as $\Delta t \to 0$ gives:

$$\frac{dp_n(t)}{dt} + \lambda p_n(t) = \lambda p_{n-1}(t). \qquad (2)$$

The solution of this difference-differential equation is the Poisson probability density:

$$p_n(t) = \frac{(\lambda t)^n}{n!} e^{-\lambda t}. \qquad (3)$$

The average or expected number of spike occurrences, $\bar{n}$, during time t is given by:

$\bar{n} = \lambda t.$

The variance of spike occurrences is also equal to λt, so:

$\sigma^2 = \bar{n}.$

If the actual number of spikes detected in an EEG record of length t is N, then to test significance we need to determine the likelihood that N or more spikes could occur in a normal EEG record. This is given by the cumulative distribution:

$$P_N(t) = \sum_{n=N}^{\infty} \frac{(\lambda t)^n}{n!} e^{-\lambda t}$$
$$= 1 - \sum_{n=0}^{N-1} \frac{(\lambda t)^n}{n!} e^{-\lambda t}. \qquad (4)$$

If N is large compared to $\bar{n}(=\lambda t)$, then the likelihood computed from Equation (4) is small. If this likelihood is sufficiently small, then we reject the hypothesis that an EEG record containing N spikes in a time t is a normal record.

For several values of spike-count expectation, the level of significance associated with this hypothesis for a record with N spike indications can be obtained from plots of the cumulative distribution shown in Figure 1. For example, if the expected number of spikes over a given length of a normal record is 6, then the plot shows that the probability of 18 spikes occurring in a normal record is 0.0001. Therefore, the hypothesis that an EEG in which 18 spikes are detected represents a normal subject is rejected at the 0.0001 level. The detection of 12 spikes would allow rejection of the hypothesis at the 0.02 level.

It should be pointed out that such statistical modeling of multiple detections over long EEG records is essential because of the false signals, artifacts, and the many uncontrollable sources

of physiological interference that plague the evaluation of EEGs. These statistical procedures follow and supplement the digital filtering procedures used in designing the detector, as outlined in the previous sections and described in our publications.

DETECTION OF SPIKE CORRELATED SCALP TRANSIENTS OF UNKNOWN WAVESHAPE

An alternate approach to the deep spike noninvasive detection problem is required when the recurring scalp EEG transient pattern is of unknown waveshape. Since averaging methods for visualizing a recurrent waveshape in noisy EEG require that the averaging process be synchronized by the deep spike event which can be detected only by invasive methods, the waveshape of the recurrent transient is frequently unknown. Under these conditions, the methodology[4][5] for detecting the presence of a recurrent complex transient in scalp recorded brain electrical activity is based on the application of deconvolution procedures as described below.

A recurrent transient waveform in the EEG can be represented as follows:

$$E(t) = \sum_{k=0}^{n} A_k X(t-\tau_k) + N(t) \qquad (5)$$

Alternatively, (5) may be written as a convolution product:

$$E(t) = X(t) * \sum_{k=0}^{n} A_k \, \delta(t-\tau_k) + N(t) \qquad (6)$$

where * designates convolution, and

$X(t)$ = intermittent pattern; i.e., waveshape of recurrent transient

$N(t)$ = EEG background activity

$\delta(t-\tau_k)$ = Dirac delta function at τ_k

The deconvolution of the convolution factors in equation (6) is accomplished in several steps. First, the Fourier transform of

(6) gives the algebraic product of the individual Fourier transforms of the intermittent pattern and the set of delta functions. This suggests the use of cepstral analysis which involves computation of the logarithm of the Fourier transform as a second step and, as a third step, computation of the inverse Fourier transform of this result to produce a function called the cepstrum. The properties of the cepstrum will reveal the presence of a recurrent pattern in the EEG by virtue of spikes which will appear in the cepstrum when two or more recurrences of the pattern are embedded in the EEG epoch analyzed.

If the waveform characteristics are of interest, then this methodology can also be used to determine the shape of the transient pattern. This is accomplished by smoothing the cepstrum to eliminate the spikes, and then reversing all the transformations used to produce the cepstrum. However, this is a difficult computational problem and it is possible to circumvent these procedures if one is not interested in ascertaining the shape of the pattern, but simply in detecting whether a recurrent pattern is contained within the time epoch analyzed. If at least two patterns are captured in the data epoch, then analysis shows that the power spectral density (PSD) will contain ripples which are attributable to the presence of the recurring pattern. The assumption underlying the utility of this approach is that the background EEG, in the absence of a recurrent transient pattern, will possess a

smooth or unrippled PSD. Figures 2 and 3 demonstrate that this assumption holds for the EEG data recorded under "eyes open" conditions from occipital leads during an experiment in which transients were introduced into the background EEG by intermittent visual stimulation. The figures show that the PSD for the no stimulus condition is smooth (Figure 2) while the PSD for the stimulus condition exhibits ripples (Figure 3) whose peaks are separated by the reciprocal of the stimulus interval.

In summary, the above results demonstrate that PSD analysis of sufficient frequency resolution to resolve ripples may provide a tool for noninvasively diagnosing illnesses in which deep brain electrical spiking may be a factor. More generally, the analytical methods described in this section provide a basis for investigating the clinical implications of weak recurrent transients which are embedded in EEG background and therefore usually not discernible by visual inspection of the EEG time series.

EEG SPECTRAL COHERENCE

Spectral coherence analysis of the EEG provides a frequency dependent measure of shared* electrophysiological activity. Thus, if linearly related (i.e., coherent) electrophysiological activity between two EEG channels is present in a restricted portion of the frequency spectrum while the remainder of the spectrum contains activity which is linearly independent (i.e., incoherent) then the spectral coherence function by virtue of its frequency dependence, can detect coherent activity even in situations where intense levels of incoherent activity dominate the energy spectrum. Since differences in shared EEG activity may reflect differences in neural connectivity (i.e., communication between brain regions) this measure (coherence) has been adopted by several investigators[7] as a logical approach to the study of brain function in projects dealing with EEG correlates of cognition and learning disability.

PROBABILITY DISTRIBUTION OF COHERENCE ESTIMATES

The coherence function (i.e., Spectral Coherence) is defined in terms of the normalized cross-spectrum of two time series. The cross-spectrum is defined as the Fourier Transform of the cross-correlation function, viz:

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*In this context shared electrophysiological activity among brain regions is defined as that activity at a recording site that is related to the activity at another recording site through a linear transformation.

Denote, $S_1(t)$, $S_2(t)$ $\equiv$ different time series

$\phi_{12}(\tau)$ $\equiv$ cross-correlation function of $S_1(t)$, $S_2(t)$, where τ is the variable time shift between S_1 and S_2, and $\phi_{12}(\tau)$ is defined by the integral equation (7)

$$\phi_{12}(\tau) = \frac{1}{T} \int_0^T S_1(t)\ S_2(t + \tau)dt \tag{7}$$

Then denote, $P_{12}(f)$ $\equiv$ cross-spectrum of $S_1(t)$, $S_2(t)$ where $P_{12}(f)$ is defined by (8), using the exponential form of the Fourier transformation.

$$P_{12}(f) = \int_{-\infty}^{+\infty} \phi_{12}(\tau)e^{-i2\pi f\tau}d\tau \tag{8}$$

(where f is frequency in hertz and τ is time shift in seconds)

By substituting equation (7) into equation (8) and appropriately factoring the resulting double integral it can be shown that

$$P_{12}(f) = \overline{S}_1(f)\ \overline{S}_2^c(f) \quad (c \text{ denotes complex conjugate}) \tag{9}$$

where: $\overline{S}_1(f)$ is the Fourier transform of $S_1(t)$ and $\overline{S}_2^c(f)$ is the conjugate Fourier transform of $S_2(t)$. Note that $\overline{S}_1(f)$ and $\overline{S}_2^c(f)$ are complex numbers in general and therefore so is $P_{12}(f)$. We may represent them in polar form, as follows:

$$\overline{S}_1(f) = r_1e^{i\theta_1} \tag{10}$$

$$\overline{S}_2^c(f) = r_2e^{-i\theta_2} \tag{11}$$

Substituting (10) and (11) into (9) gives the cross-spectral density in polar form:

$$P_{12}(f) = r_1 r_2 e^{i(\theta_1-\theta_2)} = r_1 r_2 e^{i\theta} \tag{12}$$

(where $\theta = \theta_1 - \theta_2$)

While not explicitly shown, note that the r's and θ's are functions of f. Now to arrive at the spectral coherence function we normalize equation (12) by dividing by $r_1 r_2$ and then averaging over a number of frequencies and/or averaging over a number of time epochs of the two time series being analyzed.

Thus if the average is taken over $2N + 1$ discrete frequencies we may write the spectral coherence as

$$C(f_o) = \frac{1}{2N+1} \sum_{k=-N}^{N} e^{i\theta(f_k)} \tag{13}$$

where f_o is the center of the spectral window and uniform weighting is used in the window. If the average is taken over M time epochs (ensemble averaging) we may write the spectral coherence as

$$C(f_k) = \frac{1}{M} \sum_{m=1}^{M} e^{i\theta_m(f_k)} \tag{14}$$

If a combination of frequency and ensemble averaging is used then spectral coherence may be written

$$C(f_o) = \frac{1}{M(2N+1)} \sum_{m=1}^{M} \left(\sum_{k=-N}^{k=N} e^{i\theta_m(f_k)} \right) \tag{15}$$

Again these expressions assume the use of uniform weighting in the spectral window.

It should be noted that for linearly independent signals the phase difference $\theta(=\theta_1-\theta_2)$ is a random function over both frequency and ensemble and therefor the expected value of coherence

averaged over frequency and/or time (ensemble averaging) is zero.

Thus, when coherence deviates significantly from zero, one may conclude that the two signal processes in question are related through a linear transformation over the spectral region where such significant deviation occurs.

The statistical measure of significance of a particular coherence estimate depends on the number of independent samples of coherence which are used in arriving at the coherence estimate, and upon the probability distribution function of these coherence estimates as described below.

A coherence estimate is the average computed from independent samples of the normalized cross-spectrum. These samples can be represented as points on the unit circle in the complex plane, as illustrated in Figure 4. If these points are uniformly distributed over the unit circle, it is clear that the expected value of coherence lies at the origin ($\bar{x} = \bar{y} = 0$). The normalized samples of cross-spectrum may be written:

$$x_k + iy_k = e^{i\theta_k} = \cos\theta_k + i \sin \theta_k$$

The distribution shown in Figure 4 is equivalent to stating that the relative phase values between S_1 and S_2 at frequency f_0 are uniformly randomly distributed over an ensemble of time epochs and/or over a number of frequencies in a spectral window centered at frequency f_0. The complex value of coherence may be written:

$$Coh(f_o) = \frac{1}{N}\sum_{k=1}^{N} x_k + i\,\frac{1}{N}\sum_{k=1}^{N} y_k \tag{16}$$

Since x_k and y_k lie on the unit circle..

$$x_k = cos\theta_k$$

$$y_k = sin\theta_k$$

the PDF (Probability Distribution Function) of both x and y (given that θ is a uniformly distributed random variable) have the same form and are given by:

$$D(x) = \frac{1}{\pi\sqrt{1 - x^2}}, \quad D(y) = \frac{1}{\pi\sqrt{1 - y^2}} \tag{17}$$

The corresponding means, $(\bar{x}, \bar{y})$ and variances (σ_x^2, σ_y^2) are given by

$$\bar{x} = \bar{y} = 0 \tag{18}$$

$$\sigma_x^2 = \sigma_y^2 = \frac{1}{2N} \tag{19}$$

where N = number of samples.

From (18) and (19) it follows that the mean and variance of the coherence magnitude $(|coh(f_o)| \equiv r)$ is given by:

$$\bar{r} = 0 \tag{20}$$

$$\sigma_r^2 = \frac{1}{N} \tag{21}$$

Thus, to test the hypothesis that $S_1(t)$ and $S_2(t)$ are linearly independent time series, one examines the probability that the empirically-obtained mean, computed from N samples, deviates from the expected value (zero in this case). The number of standard

deviations by which the empirical value exceeds the expected value determines the level of significance.

For example when the coherence magnitude, r, is obtained by a combination of ensemble averaging over 20 epochs and frequency averaging over 5 spectral components then

$$N = 20 \times 5 = 100$$

and the resulting standard deviation of the estimate is

$$\sigma_r = \frac{1}{\sqrt{N}} = \frac{1}{\sqrt{100}} = 0.1$$

Thus an empirically obtained value of coherence magnitude which exceeds 0.2 would be more than two standard deviations from the expected value for independent signals. Therefor it would be statistically reasonable to conclude that the signals in question are not independent, but rather that they are linearly dependent or coherent over the spectral region where the coherence magnitude exceeds 0.2. At TRIMS this method of coherence analysis has been applied to a pilot study of reading disabled children and normal controls. Our initial findings suggest that bilateral EEG coherence at frequencies above 20hz is significantly lower in reading disabled children than in normal readers, which may be attributable to reduced sharing or communication between hemispheres at those frequencies. In any event this EEG measure provides a basis for comparing activity which visual examination of the EEG is incapable of discerning because the lower frequency energy which dominates

both channels conceals the coherent relationship at high frequencies. The application of coherence analysis to problems in electrophysiology is likely to grow in importance because of the need to examine the relationships among multiple channel activity which may reveal abnormalities that cannot be found in analysis of single channel properties of the EEG.

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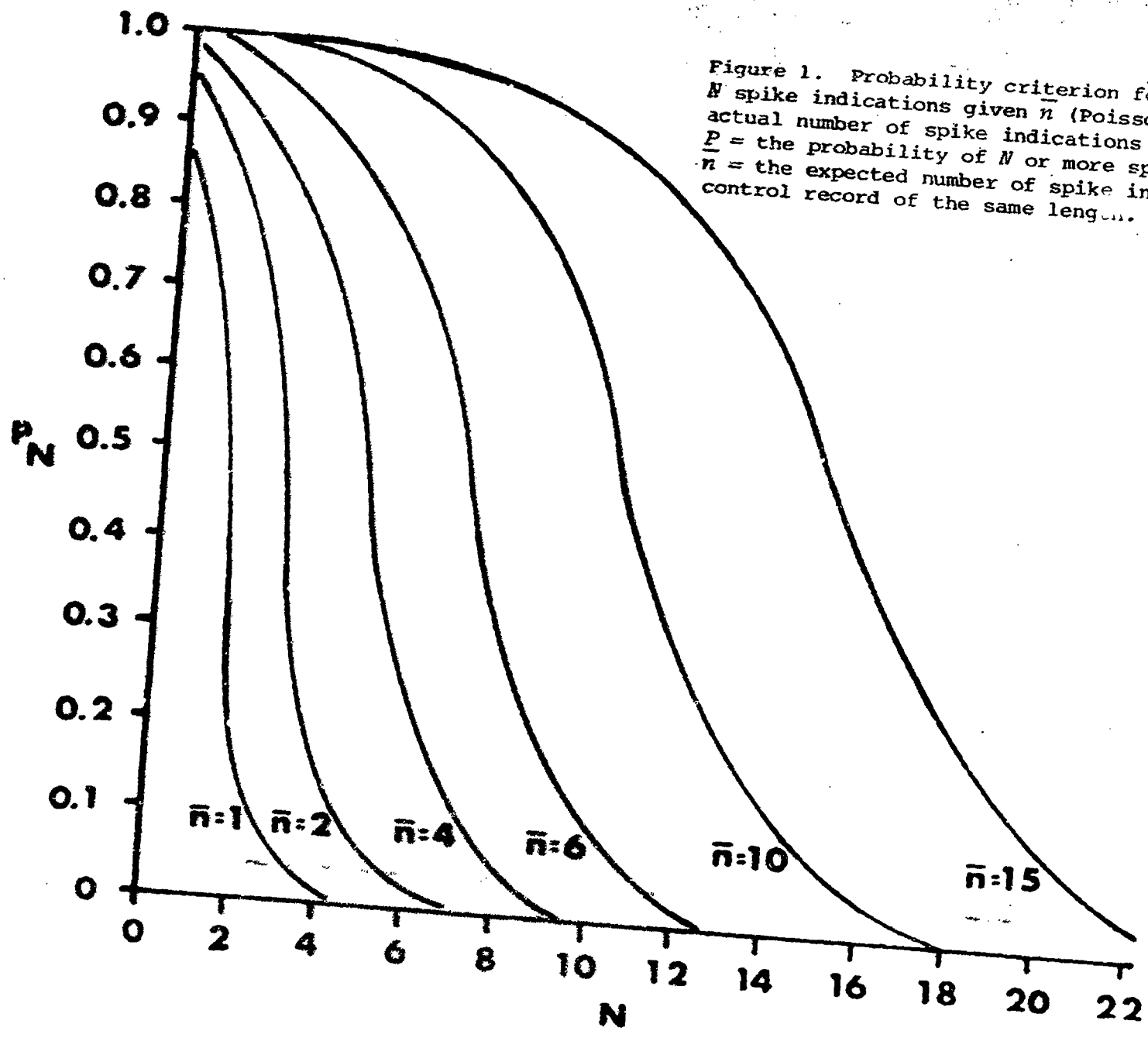

Figure 1. Probability criterion for the significance of N spike indications given $\bar{n}$ (Poisson Model). N = the actual number of spike indications in a given EEG recording, P = the probability of N or more spike indications, and $\bar{n}$ = the expected number of spike indications in a normal or control record of the same length.

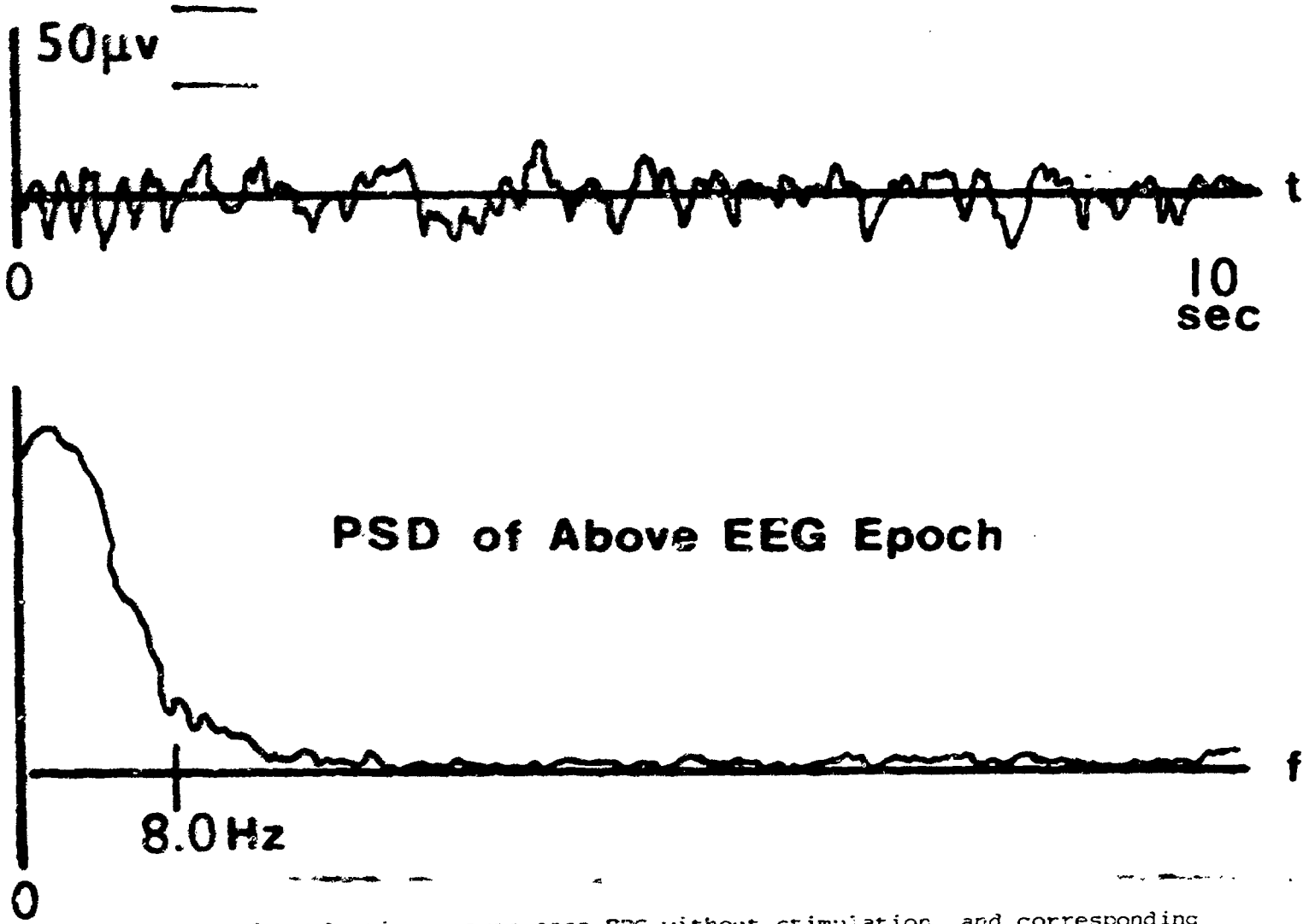

Figure 2. - Resting - eyes open EEG without stimulation, and corresponding Power Spectral Density.

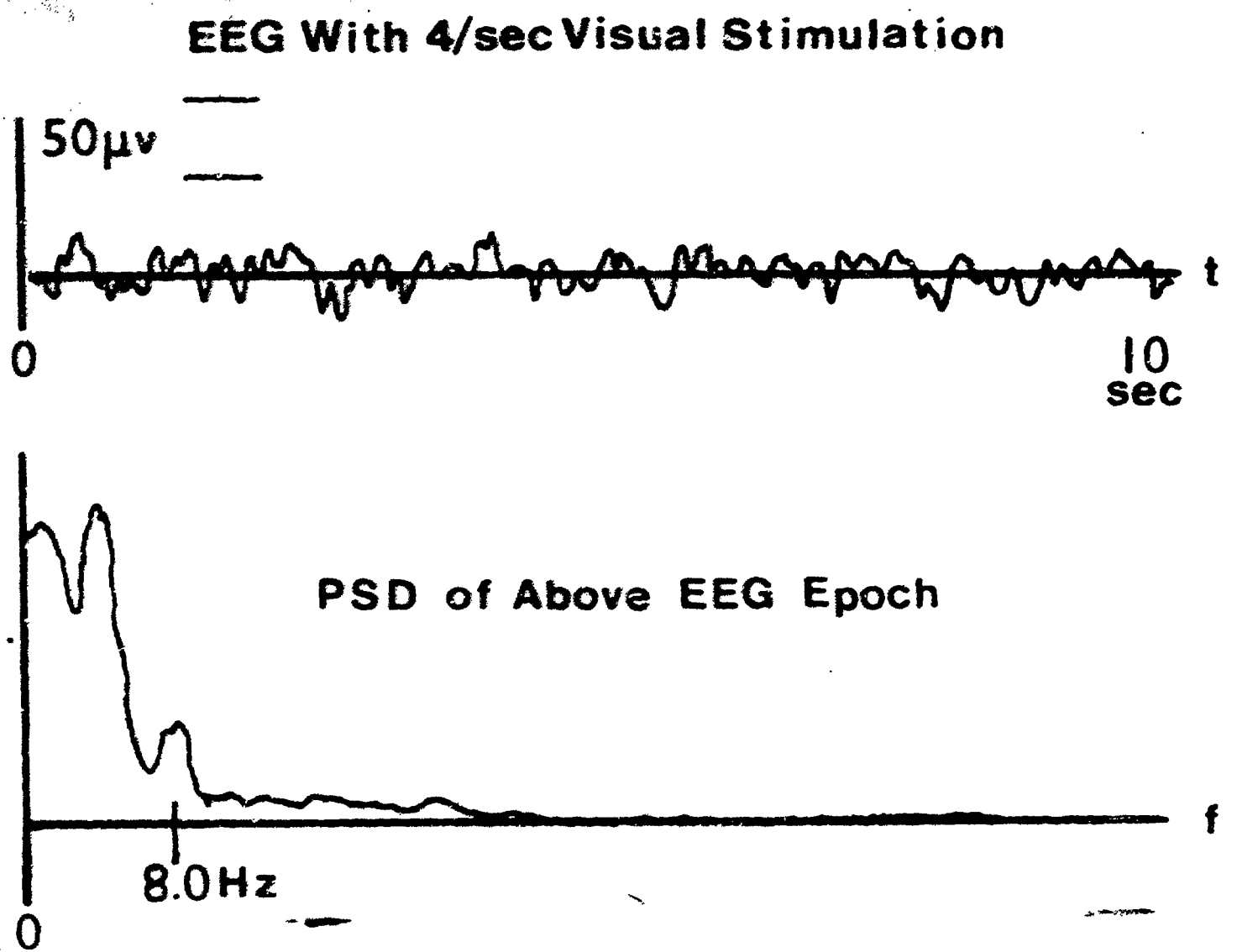

Figure 3. - Resting - eyes open EEG with 4/sec visual stimulation and corresponding Power Spectral Density.

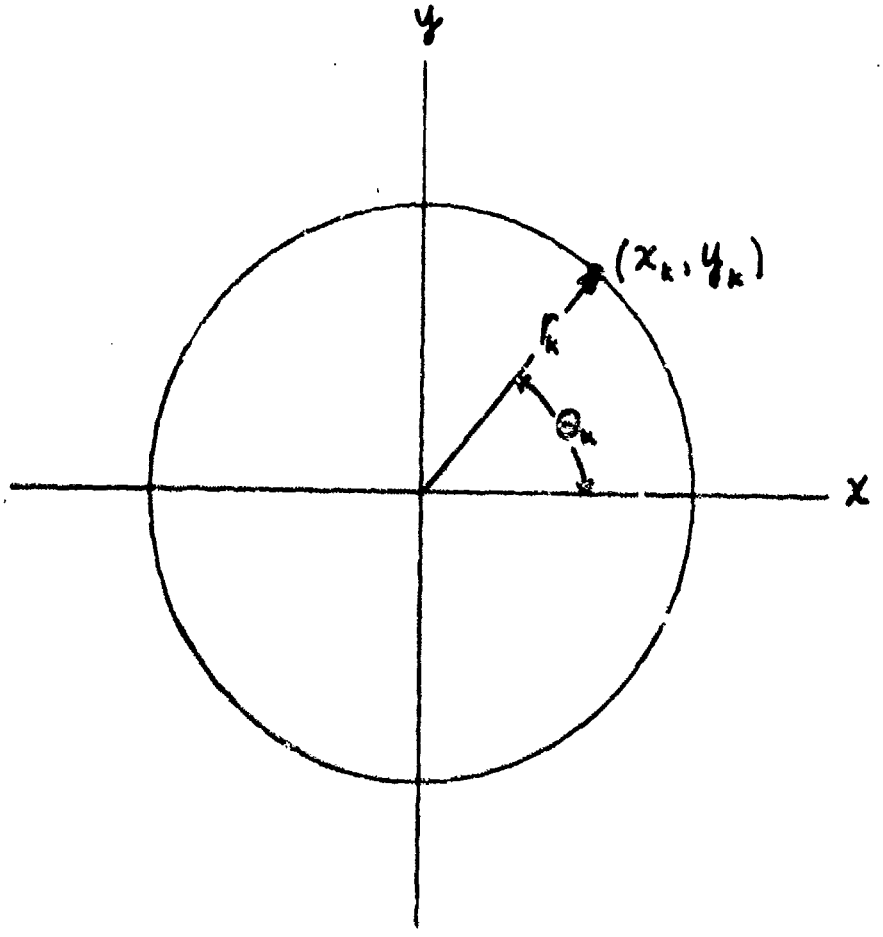

Figure 4. A coherence sample as a point on the unit circle in the complex plane. A coherence estimate is the average of such samples over a specified number of frequencies and/or a specified number of time epochs.